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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,485	12/08/2000	Erwin Ludo Roggen	6067.200-US	2466

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NOVOZYMES NORTH AMERICA, INC.
500 FIFTH AVENUE
SUITE 1600
NEW YORK, NY 10110

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 09/10/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,485	ROGGEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

Claims 1-20 are pending in the application. Claims 21-68 have been cancelled in the Preliminary Amendment of 12/8/00.

Specification

The disclosure is objected to because of the following informalities: spelling errors too numerous to mention specifically, example of such errors are: "epitopee" at page 60, line 21 and "satured", line 24; "speciec-spcific" at page 61, line 11; "blanc" at Figs. 2 and 3. Also, grammatical errors, for example, "wherein the spatial array of is a microtiter plate", page 45, line 12.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enzyme, does not reasonably provide enablement for the broadly claimed method using a library of protein variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed method drawn to screening a library of protein variants for functional variants with reduced antibody(Ab) binding capacity comprising the steps of generating a diversified library of proteins variants starting from a relevant protein backbone, transforming the library into a suitable host cell, culturing the host cells, sampling and analyzing is broader in scope than the enablement provided in the specification. The specification merely provides a laundry list of each of the components present in the method. But does not teach how the laundry list of the components are each used in the method. The illustrative Example provided in the specification to support the enabling disclosure for the broad scope of the claimed method is insufficient. The experiments provided therein are directed to a single library with no known

functionality and uses different terminologies that is confusing as it is not apparent as to which one is being referred to. The results are alleged to be given in the drawing Figures. However, there is no explanation of the results in the drawings and it is not clear as to the numbers provided therein. Also, the Example relies on numerous trademark products; the components therein are not even described. The nature of the invention is so complex and unpredictable. A library of protein variants used in the method will include millions of complex or combinations of different proteins. Without any limitations imposed by the method in the library as to e.g., its size, length and/or modifications, its deleterious effects on a host cell and other unpredictable effects and/or factors encountered by skilled in the area, the method amounts to nothing but an invitation to experiment. All studies or experiments done to date are on a case-to-case basis. Even a simple condition such as temperature, sampling method or sample size or concentration is known to affect the study on hand. Thus, the inadequate enabling disclosure for a method using a single library and mere listing of the different components are insufficient to enable the broad scope of the claimed method and the specification has not demonstrated or disclosed, otherwise. While presumably the persons in the art are highly skilled, nevertheless, the art is

so unpredictable that one cannot predict from a single embodiment its applicability to the broad scope of the present claims. The determination of even a single parameter in the method claim e.g., the diverse library of protein variants will entail undue amount of experimentation. The direction and guidance provided therein are inadequate for the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 1 is indefinite in that the preamble of the method recites for screening a library of protein variants but fail to recite a screening step in the body of the claim. Furthermore, the claim is confusing in that two (2) statutory subject matters are included in the single method i.e., the method of generating (i.e., making) and a method of analyzing (screening) for a protein variant. These two methods cover different method steps. It is not clear within the claimed

context how step (i) is accomplished since it appears that some essential steps are omitted. The following terms: "reduced", "diversified", "relevant", "suitable", "sampling" and "capacity" are relative terms which render the claim indefinite. These terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

B). Claim 2 is redundant in reciting twice for assaying for the function of the protein variants. In the context of the claim, is assaying different from analyzing the function of the protein variants? In assaying of the function, are all of the culture host cells assayed for the function? The metes and bounds of the claimed assay steps are indefinite since the method steps of assaying omit some essential steps.

C). Claim 3 is indefinite in the recitation of a "colony-picker". Within the claimed context, it is not clear whether this refers to an individual, a machine or to a colony per se? How does a colony-picker picks for a selected host cells expressing functional protein variants, especially since the metes and bounds of either the function of the protein variants or the protein variants per se are not clearly set forth?

D). Claim 4 is indefinite in that if diversity is in the epitope area, is the library used for testing for antibody binding or for the function of the protein variants? Furthermore, the metes and bounds of the epitope **areas** are indefinite as to the restrictions of said area e.g., the maximum number, location and other features of the areas in which diversity is made.

E). Claim 5 broadens the base claim 1. The base claim 1 does not recite for the protein variants modifications by single or a combination of the different recited modifications. The alternativeness of the recited modifications is indefinite as to which different combinations or the single modification is made to the protein variants. Furthermore, the use of variants and diversity of the protein library, within the claimed context, provides for confusion and ambiguity as to whether these are different or the same.

F). Claim 6 is indefinite as to the location or kind or number of additional post-translation modification site made to the protein variants. This claim broadens the base claim, which does not recite for a post-translational modification site. Also, it includes an additional step of expressing said site to a host for the corresponding in vivo modification, not found in the base claims. In the claimed context, what is considered the

corresponding *in vivo* post-translational modification of the post-translationally modified protein and what type or kind of modification can be considered post-translational that corresponds to in vivo?

G). Claim 7 is indefinite as to whether the N-glycosylation site or phosphorylation site is at the N, C or mid-portion of the protein variant, especially since these two compounds are different.

H). Claim 8 lacks antecedent basis of support from the base claim in the recitation of DNA codons at the primer level. The base claim does not recite for said DNA codons. This claim broadens the base claim. Also, it is not clear as to the maximum positions contained in more than one individual position. Within the claimed context, what is considered a **level** primer?

I). Claim 9 is indefinite in that the claim from which it depends (claim 8) does not recite for an amino acid rather, a DNA. These are two different compounds. Furthermore, claim 8 recites for a random library and is unclear as to the position, kind or location of chemical modification made that is biased to an amino acid.

J). Claim 10 is indefinite as it broadens claim 8 and unclear as to the corresponding post-translation modification recognition sequences.

K). Claim 11 is indefinite for essentially the same rejection under paragraph G, above.

L). Claim 12 is indefinite as it is not clear as to how a sequence can be predicted not to result in formation of new epitopes. Claim 8 does not recite for new epitope. Predicting or not predicting a result connotes uncertainty and fails to ascertain the claimed invention with precision.

M). Claim 13 is indefinite in that the metes and bounds of the combination of segments of known sequence is not clearly set forth. What constitutes a segment i.e., how much sequence can make up a segment or the kind of segments or combination or residues comprised therein?

N). Claim 14 is indefinite in the recitation of several discrete sites on the three-dimensional (3D) structure. What is the basis of a discrete site on the 3D structure and the metes and bounds of several numbers of these sites?

O). Claim 16 is indefinite in the requirement of a bivalent antigen-antibody interaction. There is a period at the middle of the sentence. Also, Wherein is capitalized.

P). Claim 20 broadens the base claim in reciting for a corresponding peptide-phage membrane protein fusion. The base claim does not recite for a phage protein fusion.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-73 of copending Application No. 09/417,608('608 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of screening a protein variant which comprises the broad method step (i) of generating a diversified library of protein variants starting from a relevant protein backbone encompasses the '608 method of specifically generating or producing a diversified library of protein variants.

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 11-14, 20-21 and 40 of copending Application No. 09/695,173('173 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of screening a protein variant is obvious over the '173 method of high throughput screening of a large population of host cells. The instant library which is transformed into a suitable host cells is nothing but the large population of host cells of the '173 application subjected to the same screening as the instant method. Applicants' use of the terminology of high throughput screening in the '173 is but the screening of the instant method. The method steps of the instant method drawn to screening the 3D variants of the protein is but the method steps of the '173 copending application in which the host cells are arranged in spatial array. See the instant disclosure at e.g., at page 45, lines 1-15; page 4, line 11 up to page 5,line 5 and page 48, lines 15-25 and the Title. Thus, the subject matter claimed in the instant application fully disclosed the referenced '173 copending application and would be covered by any patent granted on that copending application since the

referenced copending application and the instant application are claiming common subject matter, as stated above.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that applicants have filed several applications having one or more common inventors that appears to claim the same invention except worded differently. Applicants are required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8-10, 12-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Sosin et al (WO 99/38978).

Sosin et al discloses at page 11, line 9 up to page 12, line 18, a method of screening for a library of modified allergen (protein variants as claimed) which function by activating T cells with reduced binding capacity to IgG (reduced Ab binding capacity, as claimed) comprising synthesizing a large pool of random and defined sequences (random diversified library of protein variants, as claimed) (page 17, lines 25 up to page 20), including the modification of said allergen to decrease allergenicity (reduced antibody binding capacity), (Example 2, page 21) with the function of retaining the ability to stimulate T-cells proliferation, (Example 3, page 25 and claim 1). Sosin discloses the same recombinant method of producing the library at page 16, line 21 up to page 18, line 25 i.e., placing the cDNA into an expression vector, transfecting said vector into E. coli host cell, harvesting the cell cultures, separating the supernatant (steps iii-iv, as claimed) and applying to a resin releasing the purified protein allergen, and analyzing for the function of the protein allergen and its reduced allergenicity by binding to IgE. See further page 14, Example 1 up to page

26, Example 5, which present a detailed process steps of screening for allergen. Therefore, the specific process steps of Sosin of identifying an allergen employing a specific library and host cells fully meets or anticipates the broadly claimed method steps of screening for any protein variants exhibiting any function with a reduced antibody binding capacity comprising the broad method steps.

The selection and enrichment process using the prokaryotic cell is disclosed by Sosin and fully meets the process step of claim 2. Claims 4-5, 8-9, 12, 14-20 are disclosed by Sosin at page 17, line 25 up to page 26.

Claims 1-5, 8-10, 12-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Jespers et al (J. Mol. Biol.) or Williams et al (Jrnl. of Immunological Methods) or Collen et al (WO 96/21016).

Jespers discloses a method of screening for a protein variants, Sak antigens, comprising making a library of mutated Sak antigens displayed on the surface of filamentous phage (transformation into host cells, as claimed) that results in a reduced antibody binding without altering the function of the protein, page 713, col. 1). A positive and negative selection steps (sampling as claimed) against immobilized monoclonal and polyclonal antibodies are used to delineate dominant antigenic

determinants of Sak. In addition, mutated Sak-phages are selected from reduced antibody recognition with retention of plasminogen binding activity, (paragraph bridging pages 713-714). See the detailed steps disclosed at page 714, col. 1 up to page 716, col.2. Accordingly, the specific method steps of screening a Sak antigenic epitope as discloses by Jespers fully meets the broad claimed method of screening for any protein variants comprising the broad process steps.

Williams discloses at e.g., page 4, col. 2 up to page 15, col. 2, a method of screening for BLG comprising essentially of the steps used by Jespers that is a recombinant phage display technology, affinity sampling, reaction with antibody to detect reduced binding with retention of the function of the BLG.

Collen et al discloses a method by preparing cDNA fragment comprising at least the part of the coding sequence of staphylokinase that provides for its biological activity; performing in vitro site-directed mutagenesis on the DNA fragment to replace one or more codons for wild-type by a codon for another, cloning the mutated DNA fragments in suitable vectors, transforming a host with the vector, culturing the host cell suitable for expressing the DNA fragment. The variants have reduced immunogenicity. See page 5, line 28 up to page 7, line 20 and the Examples at page 8, Example 1. At page 20, line 14

the fibrinolytic activities of the different selected Sakstar mutants are determined (analyzing a sample by determining the function of the variant protein, as claimed). The broad claimed process steps using broad compounds are fully met by the method steps of Collen using specific components in the method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Sosin et al (WO 99/38978) or Jespers et al (J. Mol. Biol.) or Williams et al (Jrnl. of Immunological Methods) or Collen et al (WO 96/21016) (hereinafter the primary references) in view of Hewinson et al (WO 97/08322) and applicants' disclosure of known glycosylation of proteins.

Each of the primary references has been discussed, above. Each of the primary references does not disclose the modification by glycosylation or phosphorylation. However,

Hewison et al discloses that a post-translational modification as glycosylation can be used to provide proteins with a glycosylating structure that assist in the secretion from host cells that recognizes the secretion signal (page 2, line 34). Accordingly, it would have been obvious to glycosylate the peptide of each of the primary references e.g., Sosin, for the motivation provided by Hewison i.e., glycosylation is known to assist in the secretion from host cells of peptides or proteins that have been transfected in the host cell, when said host cell does not glycosylate. Said glycosylation is a post-translational modification commonly practiced in the art as disclosed by applicants in the instant disclosure at page 42, lines 23-25.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner is normally on Flexitime.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

T. D. Wessendorff
Primary Examiner
Art Unit 1627

Tdw
September 6, 2002